Synthesis and catalytic applications of an extended range of tethered Ru(II)/η^6-arene/diamine complexes.

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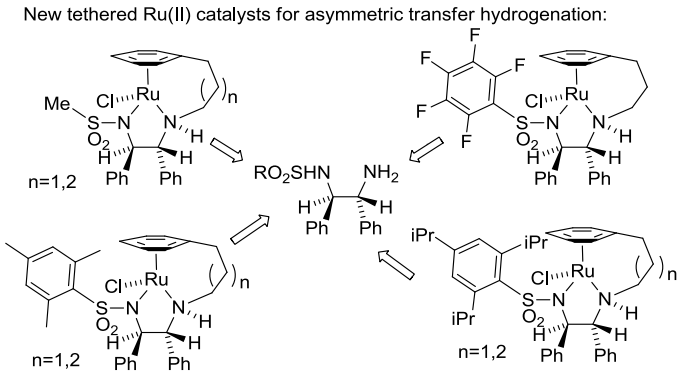
Graphic for Table of Contents Entry.



Abstract: A series of novel enantiopure Ru(II) complexes containing a chiral diamine and η^6-arene connected by a tethering group have been prepared, and were evaluated in the asymmetric reductions of a range of ketones. Changes to the level of steric hindrance and the addition of electron-withdrawing functionality on the sulfonyl group have a significant effect on the reactivity and enantioselectivity of the catalysts.

Introduction.

Ruthenium(II) / η^6-arene complexes containing a monosulfonyl-1,2-diamine ligand of general type **1** have become established as excellent catalysts for the asymmetric reduction of ketones and imines.[1-3] Although other diamines have been employed, catalysts based on N-tosyl-1,2-diphenyl-1,2-diamine (TsDPEN) are most commonly used in synthetic applications.[2,3] This versatile class of catalyst operates successfully with a range of reducing agents including isopropanol, formic acid, sodium formate (in the case of asymmetric transfer hydrogenation –ATH)[2] and, when modified with non-coordinating counterions, hydrogen gas (in the case of asymmetric pressure hydrogenation – APH).[4] Supported versions of the catalysts have also been developed.[5] The introduction of a 'tethering' group between the arene and the diamine, i.e. as depicted in structure **2,** has been shown to increase the stability and activity of the complexes, thereby allowing reactions to be completed successfully at lower catalyst loadings.[6-7] This increased reactivity also allows the catalyst to successfully reduce relatively challenging substrates, for example hindered ketones,[6f] α-chloroketones,[6b] alkynyl ketones.[6i] and unfunctionalized imines.[6l] Following the initial report on complexes **2** and **3**, and other derivatives, by this group,[6] further developments have included the reports on the synthesis and applications of ether-tethered **4**[7] and the N-tethered **5** (Figure 1).[8]

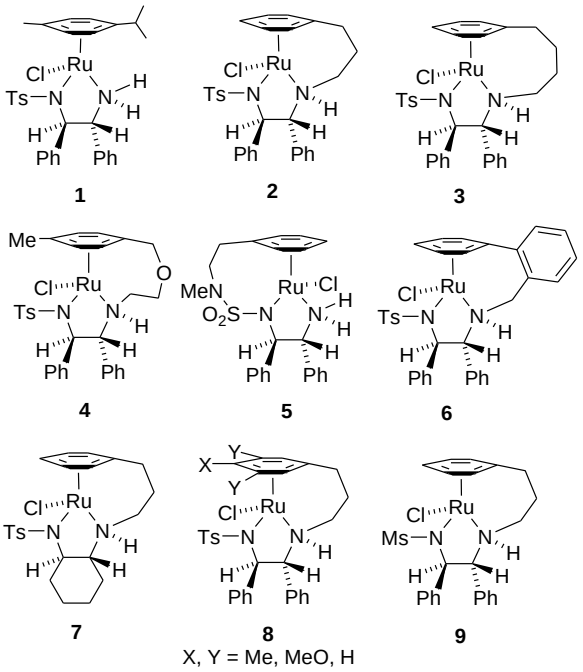


Figure 1. Catalysts for ketone reduction by ATH and APH.

In earlier work, we reported that the nature of the tethering group and the diamine may be changed, e.g. to benzyl-bridged and cyclohexyl-derived catalysts **6** and **7** respectively (Figure 1),[6d] and that the length of the tether can have a significant effect on the activity of the complexes.[6c] The effect of substitution at the arene moiety has been evaluated by synthesizing and testing catalysts such as **8**.[6h] However, with the exception the N-mesyl-substituted catalyst **9**,[6g] little research has been conducted into the effect of the systematic variation of the sulphonamide group of tethered Ru(II)/sulfonatedDPEN catalysts. In reported examples of non-tethered catalysts, this has been shown to have a significant effect. For example the use of fluoride-substituted sulfonyl groups can improve the asymmetric induction in transfer hydrogenations of a number of substrates including β-keto esters.[9] In recent examples, the use of a catalyst containing a very hindered sulfonyl group (alongside other modifications of the DPEN ligand) led to significantly improved selectivity in dynamic kinetic resolution processes.[10] Several reports have described the synthetic applications of untethered complexes containing hindered sulfonyl groups including MtsDPEN (Mts = 2,4,6-

trimethylphenyl sulfonyl) and TrisDPEN (Tris = 2,4,6-triisopropylphenylsulphonyl).[11] In some cases, for particular substrates, larger groups can afford advantages over smaller substituents. Tethered catalysts have often displayed substantially different behaviour from the non-tethered equivalents, both in terms of expanded substrate scope and choice of optimal reaction conditions. Because of this, the systematic variation of the steric and electronic properties of the sulfonyl substituents of the tethered catalysts, never before fully explored, was particularly attractive in view of the potential for providing novel and useful synthetic applications.

Results and Discussion.

As part of an ongoing research programme directed at expanding the range of available tethered complexes, we prepared a series of derivatives **2**, **3**, **9** and **10c-i** which contain a range of hindered or fluorinated sulphonamide substituents (Figure 2). The tosyl and mesyl-substituted complexes bearing a 3-carbon (3C) tether (**2** and **9**) have previously been prepared through the route described[6a-c] and their preparation was reproduced here for comparison with new complexes. The application of this route to the previously reported 4-carbon tether catalyst **3**[6c] is also described.

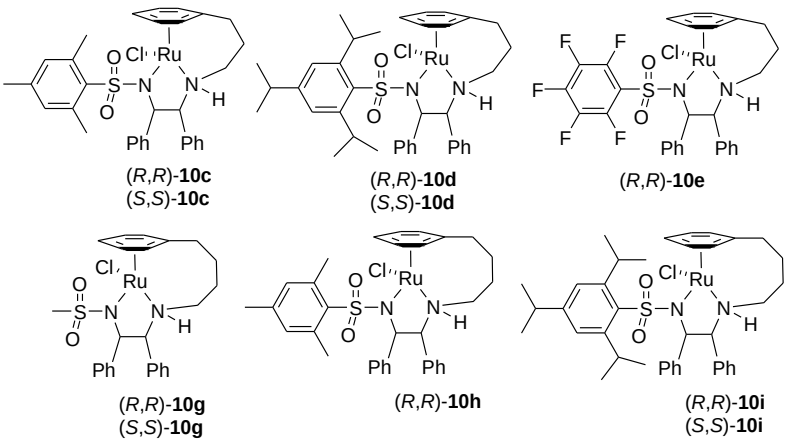


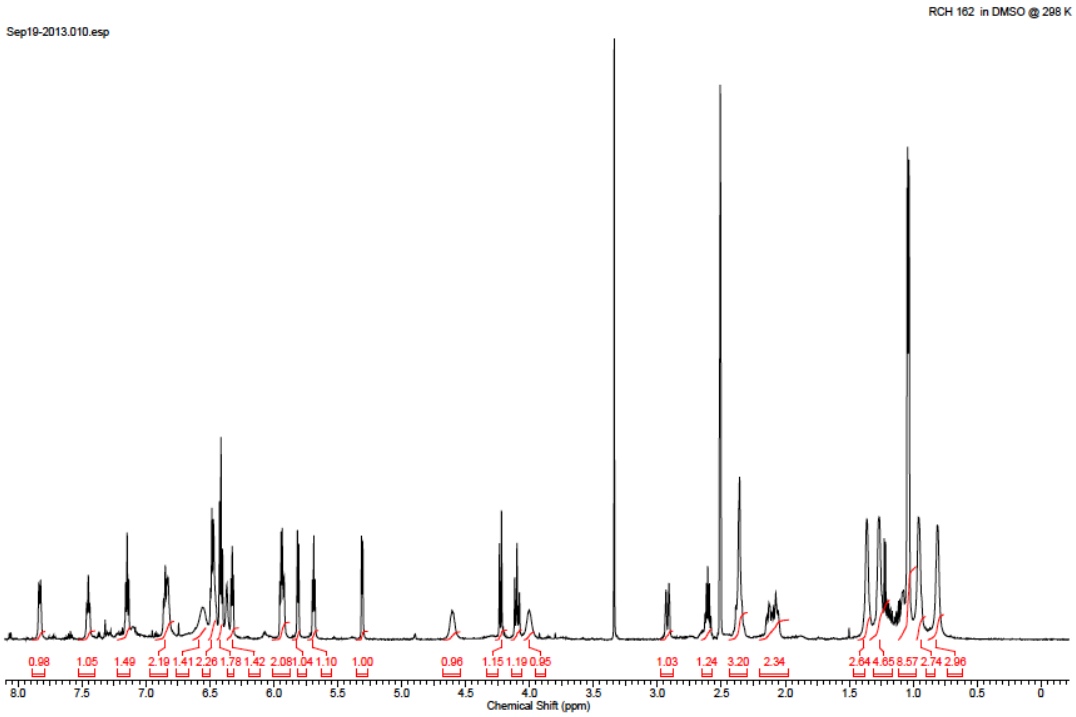
Figure 2. New Ru(II)/TsDPEN tethered catalysts with alternative sulfonyl groups.

It was decided to retain the carbon-only tether of just 3 or 4 carbons since these have already been demonstrated to be the optimal lengths in prior studies.[6-8] Although examples are given of the synthesis of a specific enantiomer of each 3C and 4C complex, samples of both enantiomers were prepared in all cases with the exception of the pentafluorophenylsulfonyl derivative **10e** and **10h**.

Following the established routes, the target complexes were prepared in good yields (Schemes 1 and 2), although the synthesis of each catalyst required individual optimisation. In the first stage of the synthesis of each of the 3C tethered complexes (Scheme 1), the diene was coupled to the required DPEN derivative via *in situ* formation of its triflate derivative,[6g] and then the resulting ligands **11a-11e** were complexed with ruthenium trichloride to give first the dimers **12a-12e** and subsequently the monomers **3, 9, 10c-e**. Good results were obtained in the complexation step through the direct use of an aqueous acidic solution of $RuCl_3$. This process avoided the need to pre-form the hydrochloride salt of the ligand, which is required when $RuCl_3.nH_2O$ is used in the complexation step, although the latter remains a viable alternative route. There is an experimental example of the use of both procedures in the Supporting Information. In the case of the MtsDPEN complex **10c**, and its TrisDPEN equivalent **10d**, the precursor ligands were prepared as the HCl salts to facilitate isolation. The dimer precursor **12d** to the TrisDPEN complex **10d** was highly soluble in ethanol but the monomeric **10d** itself was crystalline and easily isolated.

While complex 3C TsDPEN catalyst (**2**) appears as a mixture of species by ^1H and ^{13}C NMR in $CDCl_3$ but not in nitromethane-d_3,[6g] the highly hindered catalysts bearing MtsDPEN (**10c**) and TrisDPEN (**10d**) generated ^1H-NMR spectra in both $CDCl_3$ and nitromethane-d_3 showing more than one species in solution (See Supporting Information). A variable temperature analysis of the $CDCl_3$ of **10d** revealed that this ratio changed with temperature, although the peaks did not converge to one isomer. The ^1H-NMR spectrum recorded in DMSO-d_6,

however, appeared to be a single species with characteristic features that suggested a restricted rotation of the adjacent phenyl group on the diamine (Figure 3).



a)

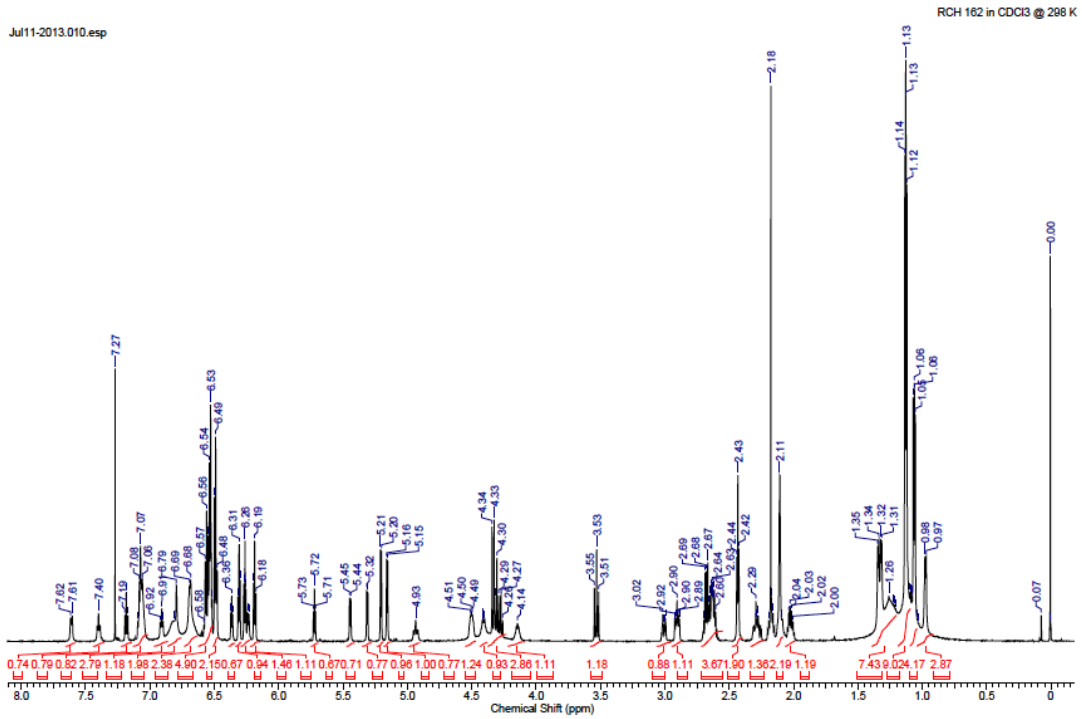
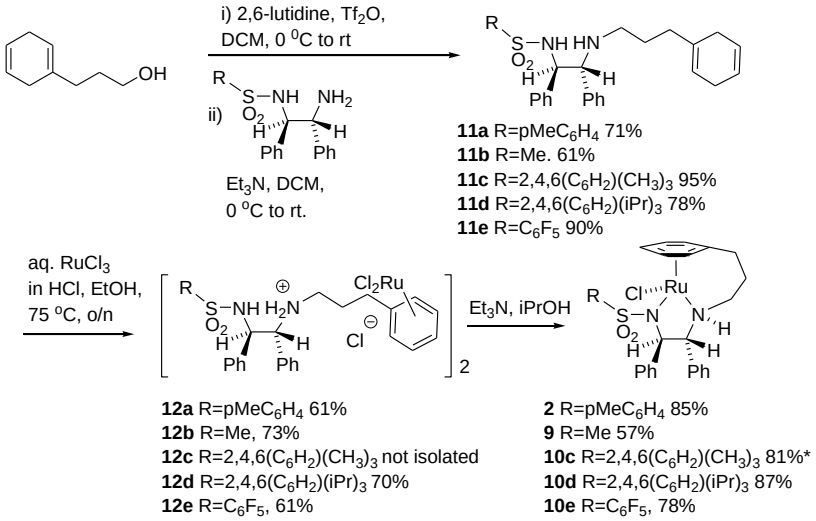


Figure 3. a) 3C-(*R,R*)-TrisDPEN monomer **10d** in DMSO. b) 3C-(*R,R*)-TrisDPEN- monomer **10d** in $CDCl_3$.

Complex **10d** could also be prepared from the dimer **12d** by treatment with Hunig's base in ethanol at temperatures as low as 20 ºC, from which the monomer precipitated directly as a red compound. Interestingly, the ^{1}H NMR spectrum of the initial product formed at 20 ºC in $CDCl_3$ appeared different to the spectrum of the product formed at 85 ºC. On the other hand the ^{1}H NMR spectrum of the crystallised product from the reaction at either temperature appeared in DMSO to be identical (see Supporting Information). Again this suggests the formation of a mixture of conformational isomers in the initial reaction, followed by isomerisation to a major isomer upon dissolution in DMSO-d_6, but not in $CDCl_3$. Accordingly, it has been found that optical rotation measured in DMSO provide opposite and equal values for enantiomeric complexes, while they differ in other solvents, suggesting that the two enantiomers of the catalysts may be present as different mixtures of isomers depending on the conditions of synthesis and isolation. As well as the presence of

conformational isomers, the possibility exists that diastereoisomers at the ruthenium stereogenic centre are formed.[12] The solvent-mediated interconversion of such conformational or configurational isomers may account for the simplification of the NMR spectra in certain solvents.[13]



* Yield is given for two steps from ligand precursor **11c**.
Mts =2,4,6-trimethylphenylsulfonyl, Tris = 2.4.6-triisopropylphenylsulfonyl

Scheme 1. Synthesis of 3C tethered complexes **2, 9, 10c-e**, (*R*,*R*) enantiomers.

The X-ray crystallographic structure of the TrisDPEN complex **10d** was obtained and served to confirm that the structure was correct (Figure 4). A feature of the structure is the *anti* arrangement of the Ru-Cl and N-H bonds, which are more commonly *cis* in such compounds.[1] However it is assumed that the Ru-H bond which subsequently forms must be *cis* to the N-H bond in order for efficient hydrogen transfer to take place to a substrate.[1] Full details of this structure and assignment of the NMR spectra are given in the Supporting Information.

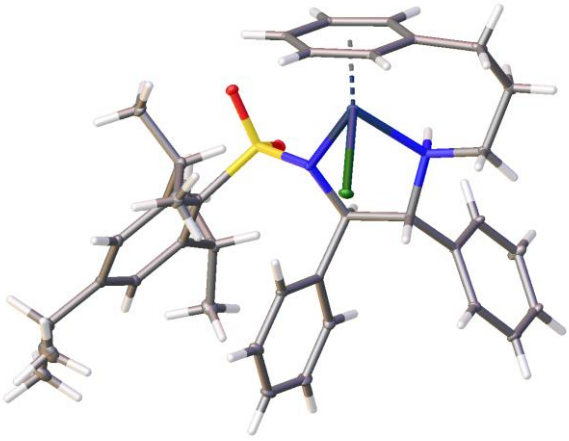
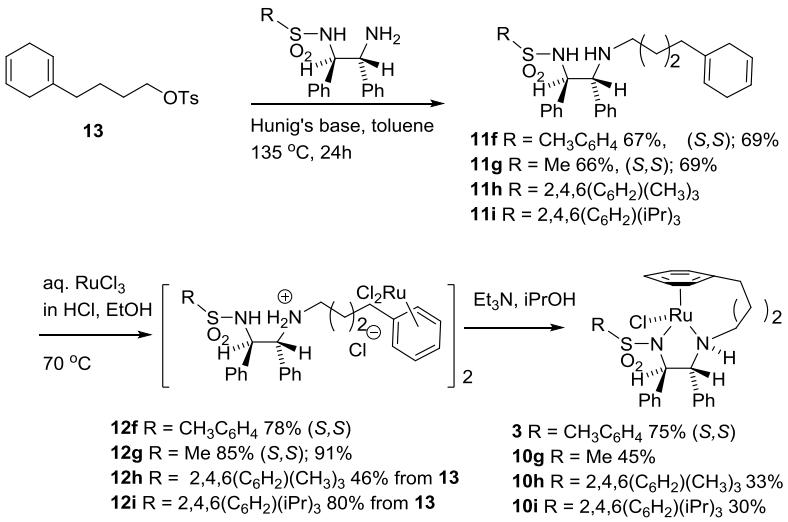


Figure 4. X-ray crystallographic structure of **10d** (CCDC 1014991).

The synthesis of the 4C tethered compounds proved to be more challenging. When alkylation of the triflate was used ('triflate method'),[6g] evidence of some aromatisation and other decomposition products of the diene were observed. Therefore the 4C tethered complexes were formed via the tosylate intermediate **13**. Treatment of the sulfonylated diamine with **13** at elevated temperature resulted in the formation of ligands **11f-11i** which were subsequently converted to the dimers upon treatment with aqueous acidic $RuCl_3$. This method worked well for the formation of the Ts, Ms and Tris catalysts **3**, **10g** and **10i** respectively, although for complex **10i** the ligand intermediate was difficult to purify due to its low polarity. Formation of the HCl salts of the 4C-tethered ligands resulted in reduced aromatisation of the diene, therefore direct conversion of the crude ligand to the dimer was preferred. Since the acidic $RuCl_3$ solution protonates the ligand immediately prior to complexation, the residence time of the salt is minimised.[14]



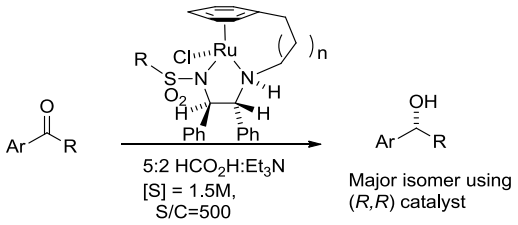
Scheme 2. Synthesis of 4C tethered complexes **3, 10g-i**. Unless otherwise stated, results for the (*R,R*)-enantiomers are shown.

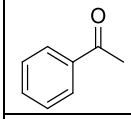
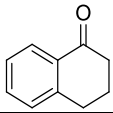
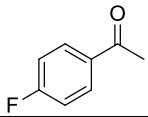
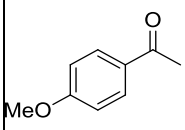
The catalysts were effective at the asymmetric transfer hydrogenation of a range of ketones using formic acid/triethylamine (FA/TEA) (Table 1). The established and commercially-available 5/2 azeotrope of formic acid and triethylamine (FA/TEA), was used throughout, and the results at a S/C of 500 and [ketone] of 1.5M are listed. In most cases, reductions were complete within 5 h at 40 °C although some of the hindered catalysts required longer reaction times and/or an increase in temperature to 60 °C (in these cases the ee value was not significantly eroded). Under these partially optimized conditions, the catalyst loadings could be reduced but with loss of activity and selectivity at lower loadings (S/C > 1000) (see the Supporting Information for a full Table). For completeness, comparisons were run against the known catalysts **2**, **3** and **9**. All catalysts worked well on acetophenone (Table 1, entry 1) and tetralone (entry 2), which are typically good substrates for ATH, generating full conversions to the alcohol products in high ee at a substrate/catalyst (S/C) ratio of 500 (0.2 mol% catalyst). In agreement with previously-reported trends, *para*-and *meta*- substituted ketones generally gave products of higher ee that the *ortho*-substituted analogues. For *para*-fluoroacetophenone (entry 3), the 4C-tethered complexes gave generally better results than

the 3C-tethered equivalents. For the *para*-methoxy (entry 4) and *para*–chloroacetophenones (entry 6), there was little variation in ee between catalysts, with the ketone containing the electron-donating substrate (MeO) being reduced more selectively although at a slower rate than that containing the electron-withdrawing Cl atom. In the case of the *ortho*- substituted acetophenones, which are known to be challenging substrates,[6h] the enantioinductions were highly variable and demonstrated the value of having an extended range of catalysts to select from. For example for the *ortho*-methoxy acetophenone (entry 5), the 4C-TsDPEN catalyst **3** gave the best result (88% ee), in sharp contrast to the established 3C-TsDPEN catalyst (70% ee) and much better than the highly hindered derivatives. For *ortho*-chloroacetophenone (entry 7), the 4C-MsDPEN catalyst (**10g**) gave the best result. Two *meta*-substituted substrates which have not been previously investigated with these catalysts provided a dramatic insight into the effect of the electronic nature of the substituent. Whilst *meta*-hydroxyacetophenone (entry 9) could be reduced in very high ee by almost all of the catalysts, the hindered ones were slightly slower. The ees for the *meta*-nitroacetophenone (entry 8) varied sharply from as low as 23% (catalyst **10d**) to a maximum of 79% (catalysts **2** and **10g**), with the very hindered catalysts giving inferior results. The results for the reductions of 3,5-dimethylacetophenone (entry 10), which are excellent, contrasts to 3,5-bis-trifluoromethylacetophenone (entry 11) where the ees were low and the sense of selectivity switched readily between catalysts. These results again highlight the detrimental effect that electron-withdrawing groups have on enantioselectivity. The ee of the 3,5-bis-trifluoromethylacetophenone reduction could be raised to as high as 81% through the use of the best catalyst, the 4C TrisDPEN complex **10i**, thus illustrating the high value of a range of diverse catalysts for investigations into specific substrates. A similar observation was made for 2-methoxy-5-fluoroacetophenone (entry 12), where catalyst **10g** proved to be the most effective. Addition of a substituent in the alkyl position, i.e. in propiophenone (entry 13),

resulted in a slower rate of reduction by the hindered catalysts, which required a higher temperature (60 ^{o}C) to reach completion, although the ee values remained consistently high and similar between the range of catalysts examined.

Table 1, Asymmetric transfer hydrogenation of ketones using catalysts **2, 3, 9, 10c-i**. The top line indicates conversion (time/h) and the lower line indicates ee.[a]



Catalyst ⇨ Entry / Ketone ⇩	T/ ^{o}C	3C Ts (*R*,*R*) **2**	3C Ms (*R*,*R*) **9**	3C Mts (*R*,*R*) **10c**	3C Tris (*R*,*R*) **10d**	3C PFB (*R*,*R*) **10e**	4C Ts (*S*,*S*) **3**	4C Ms (*R*,*R*) **10g**	4C Mts (*R*,*R*) **10h**	4C Tris (*R*,*R*) **10i**
1 	40	100 (5) 97 (*R*)	100 (5) 96 (*R*)	100 (24) 95 (*R*)	85 (24) 96 (*R*)	100 (5) 98 (*R*)	100 (5) 96 (*S*)	100 (5) 98 (*R*)	88 (24) 96 (*R*)	99 (24) 97 (*R*)
	60	-	-	-	100 (5) 94 (*R*)	-	-	-	95 (5) 98 (*R*)	-
2 	40	100 (5) 99.8 (*R*)	95 (24) 98 (*R*)	82 (24) 99 (*R*)	82 (24) 99 (*R*)	100 (5) 96 (*R*)	100 (5) >95 (*S*)	80 (5) >95 (*R*)	93 (5) >95 (*R*)	94 (24) 98 (*R*)
	60	-	-	100 (5) >95 (*S*)	98 (8) 99 (*R*)	-	-	-	-	-
3 	40	100 (5) 95 (*R*)	100 (5) 89 (*R*)	100 (24) 88 (*S*)[b]	96 (5) 84 (*R*)	100 (9) 94 (*R*)	100 (5) >95 (*S*)	100 (5) 94 (*S*) [b]	99 (24) 96 (*R*)	100 (24) 94 (*R*)
4 	40	100 (5) 96 (*R*)	100 (24) 95 (*R*)	69 (24) 93 (*R*)	37 (24) 98 (*R*)	100 (24) >95 (*R*)	96 (7) 95 (*S*)	100 (5) >95 (*R*)	42 (24) 97 (*R*)	51 (24) >95 (*R*)
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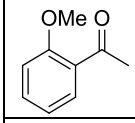
5 	40	100 (5) 70 (*R*)	91 (24) 60 (*R*)	95 (24) 33 (*R*)	94 (24) 22 (*R*)	96 (5) 74 (*R*)	100 (5) 88 (*S*)	92 (24) 83 (*R*)	79 (24) 53 (*R*)	34 (24) 52 (*R*)
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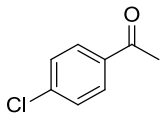
6 	40	100 (5) 91 (*R*)	100 (5) 88 (*R*)	100 (24) 87 (*R*)	97 (24) 80 (*R*)	100 (5) 91 (*R*)	100 (5) 93 (*S*)	100 (5) 87 (*R*)	96 (5) 89 (*R*)	99 (5) 89 (*R*)
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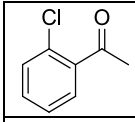		69 (*R*)	69 (*R*)	46 (*R*)	35 (*R*)	68 (*R*)	82 (*S*)	86 (*R*)	52 (*R*)	53 (*R*)
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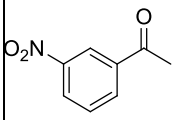
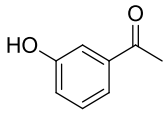
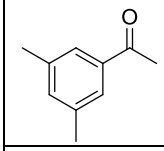
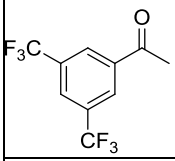
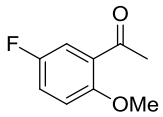
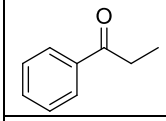
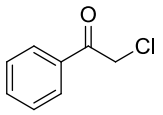
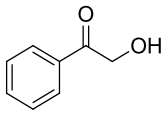
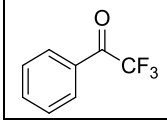
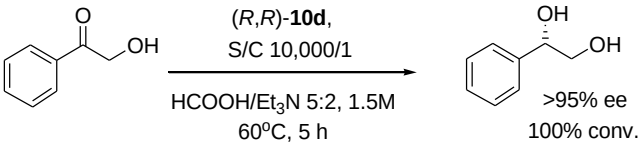
8 	40	100 (5) 79 (*R*)	100 (5) 78 (*R*)	100 (5) 47 (*S*) [b]	100 (5) 23 (*R*)	100 (5) 70 (*R*)	100 (5) 74 (*S*)	100 (5) 79 (*S*) [b]	97 (5) 56 (*R*)	98 (5) 30 (*R*)
9 	40	98 (5) 99 (*R*)	100 (7) 98 (*R*)	96 (8) 98 (*R*)	86 (8) 98 (*R*)	99 (24) 98 (*R*)	100 (5) >95 (*S*)	100 (5) >95(*S*) [b]	100 (8) >95 (*R*)	96 (5) 98 (*R*)
10 	40	100 (5) 96 (*R*)	100 (5) 92 (*R*)	94 (24) 91 (*R*)	81 (24) 86 (*R*)	99 (24) 95 (*R*)	100 (5) >90 (*S*)	100 (5) >95(*S*) [b]	90 (24) 92 (*R*)	77 (24) 93 (*R*)
	60	-	-	96 (24) 88 (*R*)	100 (24) 86 (*R*)	-	-	-	100 (24) 92 (*R*)	100 (24) 92 (*R*)
11 	40	100 (5) 56 (*R*)	100 (5) 59 (*R*)	100 (5) 65 (*S*)	100 (5) 77 (*S*)	100 (5) 41 (*R*)	100 (5) 58 (*S*)	100 (5) 60 (*R*)	82 (24) 18 (*S*)	100 (5) 81 (*S*)
12 	40	99 (3) 45 (*R*)	100 (3) 42 (*R*)	99 (6) 4 (*S*)	99 (6) 13 (*S*)	100 (6) 31 (*R*)	100 (3) 62 (*S*)	100 (3) 67 (*S*) [b]	100 (6) 19 (*R*)	98 (6) 4 (*R*)
13 	40	100 (24) 94 (*R*)	62 (24) 97 (*R*)	49 (24) 92 (*S*) [b]	29 (24) 96 (*R*)	100 (24) 95 (*R*)	-	98 (5) 93 (*S*) [b]	-	57 (24) >95 (*R*)
	60	100 (5) 95 (*R*)	100 (5) 92 (*R*)	100 (24) 91 (*S*) [b]	99 (24) 92 (*R*)	100 (5) 92 (*R*)	100 (5) 92 (*S*)	100(24) 92 (*S*) [b]	100 (24) 94 (*R*)	100 (24) 96 (*R*)
14 	40	85 (1) (11)[c] >95 (*S*)	72 (3) (22) [c] >95 (*S*)	99 (1) >95 (*S*)	100 (1) 93 (*S*)	90 (7) (10) [c] >95 (*S*)	96 [d] (1) 96 (*R*)	100 (1) >95 (*S*)	100 (1) >95 (*S*)	100 (1) >95 (*S*)
15 	40	100 (5) >95 (*S*)	100 (6) >95 (*S*)	100 (6) >95 (*S*)	99 (5) 96 (*S*)	100 (6) >95 (*S*)	100 (5) >95 (*R*)	0 (24) -	100 (5) >95 (*S*)	100 (6) >95 (*S*)
	60	-	-	-	99 (5) >95 (*S*)	-	-	-	-	-
16 	40	100 (5) 45 (*R*)	100 (5) 22 (*R*)	100 (5) 17 (*R*)	100 (5) 1 (*R*)	100 (5) 41 (*R*)	100 (5) 56 (*S*)	100 (5) 44 (*R*)	100 (5) 37 (*R*)	100 (5) 29 (*R*)

a. Reactions were stopped at 24h if incomplete. For details of reductions at other temperatures/loadings see Supporting Information, >95% ee is used where the minor peak could not be integrated but the retention times were not widely spread. Catalysts of (*R*,*R*)- configuration were used unless otherwise specified. b. The catalyst of (*S*,*S*)-configuration was used. c Figures in these parenthesis indicate percentage of $PhCOCH_2OCHO$ that was formed in the reaction. d. ca. 4% of a side product was formed, suspected be an epoxide.

For α-chloroacetophenone (entry 14), the ees of the reduction products were consistently high. While significant activity could be retained at S/C as high as 5,000 without loss of enantioselectivity (see Supporting Information), significant amounts of α-formatoacetophenone was formed as a side product.[15] It was noteworthy that the cleanest reductions of α-chloroacetophenone were achieved using the 4C tethered complexes **10g-10i** , which still retained the high reaction rates typical of this class of catalyst, delivering products in >95% ee in each case. Excellent results were also obtained using α-hydroxyacetophenone (entry 15) as substrate, which was reduced rapidly by most catalysts at 40 ^{o}C (ca. 5h reaction time for full reduction) and consistently in very high ee. In extended studies, it was found that several complexes could deliver high conversions to product at loadings as low as S/C = 10,000, when reactions were run at 60 ^{o}C (see Supporting Information), but still in >95% ee. Of these, the 3C TrisDPEN catalyst (**10d**) was the most promising, giving full conversion within 5h, to the alcohol in >95% ee (Scheme 3). An interesting exception was the lack of reactivity of catalyst **10g** towards this substrate, despite repeated attempts, indicating that a very specific interaction may be operating between the ketone and the relatively unhindered catalyst.



Scheme 3: ATH of α-hydroxyacetophenone

Finally, in the case of 1,1,1-trifluoroacetophenone (entry 16), the enantioinduction was low, as has previously been observed due to the competition between CF_3 and Ph for the position adjacent to the η^6-arene ring in the transition state.[3j,6k,11d] The major enantiomer in

most of the other cases corresponded consistently to that which would be predicted based on the known enantioselectivity of this class of catalyst.[1-3,6e]

Conclusions

In conclusion, we have prepared a series of diverse novel tethered Ru(II) complexes for application to the asymmetric transfer hydrogenation of ketones. In several cases, the availability of structurally different members of the family of tethered catalysts has proven to be advantageous for identifying the best match with particular substrates. Both the substitution at the sulphur and the length of the tether (3C or 4C) have been shown to influence activity and enantioselectivity for the reductions of several substrates, with the extent of this effect being dependent on the nature of the substrate itself. The complexes bearing bulky sulfonyl groups, in particular, have emerged as robust and versatile new catalysts.

Supporting Information

Experimental details, NMR spectra, ee determination data and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTES

The authors declare no competing financial interests.

ACKNOWLEDGMENTS

The authors thank the Technology Strategy Board (TSB, DTI technology project No: 101330 Reference: 19201-138226) and Johnson Matthey Catalysis and Chiral Technologies (JM CCT) for funding. The X-ray crystallographic data for complex **10d** was collected on an Oxford Diffraction Gemini instrument obtained through the Science City Project with support from Advantage West Midlands and part funded by the European Regional Development Fund. S. Davis, I. Harvey, A. Rajakarier and D. Bargh of Alfa Aesar (a Johnson Matthey company) are thanked for the development of the manufacturing processes for the preparation of mono-sulfonylated DPEN ligands used as precursors in this project.

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